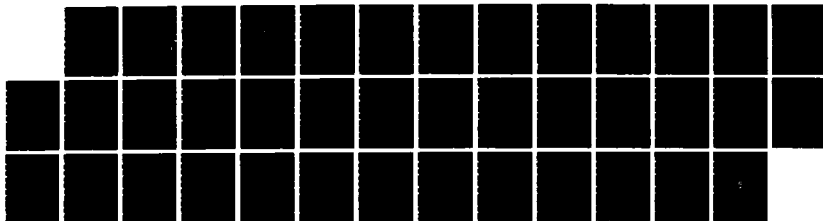
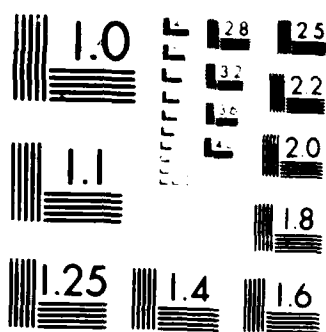


NO-A176 956 STATISTICS FOR THE TWO-SAMPLE SURVIVAL ANALYSIS PROBLEM 1/1
BASED ON PRODUCT (U) NORTH CAROLINA UNIV AT CHAPEL
HILL CENTER FOR STOCHASTIC PROC M O'SULLIVAN ET AL.
UNCLASSIFIED NOV 86 TR-163 AFOSR-TR-87-0035 F/G 12/1 ML





U.S. GOVERNMENT PRINTING OFFICE: 1963

UNCLASSIFIED

SECURITY CLASSIFICATION OF THIS PAGE

②

REPORT DOCUMENTATION PAGE

1a. REPORT SECURITY CLASSIFICATION UNCLASSIFIED		1b. RESTRICTIVE MARKINGS	
2a. SECURITY CLASSIFICATION AUTHORITY NA		3. DISTRIBUTION/AVAILABILITY OF REPORT Approved for Public Release; Distribution Unlimited	
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE NA			
4. PERFORMING ORGANIZATION REPORT NUMBER(S) Technical Report No. 165		5. MONITORING ORGANIZATION REPORT NUMBER(S)	
6a. NAME OF PERFORMING ORGANIZATION University of North Carolina	6b. OFFICE SYMBOL (If applicable)	7a. NAME OF MONITORING ORGANIZATION AFOSR/NM	
6c. ADDRESS (City, State and ZIP Code) Center for Stochastic Processes, Statistics Department, Phillips Hall 039-A, Chapel Hill, NC 27514		7b. ADDRESS (City, State and ZIP Code) Bldg. 410 Bolling AFB, DC 20332-6448	
8a. NAME OF FUNDING/SPONSORING ORGANIZATION AFOSR	8b. OFFICE SYMBOL (If applicable) NM	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER F49620 85 C 0144	
8c. ADDRESS (City, State and ZIP Code) Bldg. 410 Bolling AFB, DC		10. SOURCE OF FUNDING NOS.	
		PROGRAM ELEMENT NO. 6.1102F	PROJECT NO. 2304
		TASK NO. A5	WORK UNIT NO.
11. TITLE (Include Security Classification) Statistics for the two-sample survival analysis problem based on product limit estimators			
12. PERSONAL AUTHOR(S) of the survival functions" O'Sullivan, M. and Fleming, T.R.			
13a. TYPE OF REPORT technical preprint	13b. TIME COVERED FROM 10.86 TO 9.87	14. DATE OF REPORT (Yr., Mo., Day) November 1986	15. PAGE COUNT 33
16. SUPPLEMENTARY NOTATION			
17. COSATI CODES FIELD GROUP SUB GR XXXXXXXXXXXXXXXXXXXX		18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number) Keywords: N/A	
19. ABSTRACT (Continue on reverse if necessary and identify by block number) A class of statistics for the two-sample survival analysis problem is introduced. The SW-statistic may be written as the integral of a weighted difference in the estimated survival functions, the integral being with respect to Lebesgue measure on time. Since the integral is with respect to real-time the statistics are not generalized rank-statistics. However, with an appropriate choice of weight function they are non-parametric in the sense that weak convergence is guaranteed for any underlying configuration of survival and censoring distributions.			
20. DISTRIBUTION/AVAILABILITY OF ABSTRACT UNCLASSIFIED/UNLIMITED <input checked="" type="checkbox"/> SAME AS RPT <input type="checkbox"/> DTIC USERS <input type="checkbox"/>		21. ABSTRACT SECURITY CLASSIFICATION UNCLASSIFIED	
22a. NAME OF RESPONSIBLE INDIVIDUAL Deborah A. Heston	22b. TELEPHONE NUMBER (Include Area Code) 919-962-2307	22c. OFFICE SYMBOL AFOSR/NM	

COPY FILE

UNCLASSIFIED

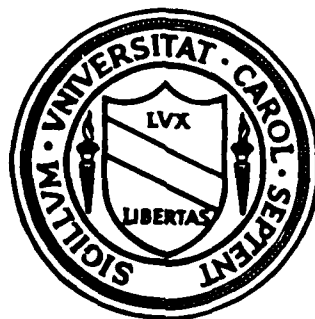
*19 cont'd.

Asymptotic distribution theory under the null is derived. Consistency under a fixed alternative is shown. Efficacy expressions under natural sequences of local alternatives are given and an expression for the most efficient weight function is developed. The asymptotic efficiencies of some specific SW-statistics under the proportional hazards alternative are examined.

CENTER FOR STOCHASTIC PROCESSES

AFOSR-TR. 87-0035

Department of Statistics
University of North Carolina
Chapel Hill, North Carolina



Approved for public release; distribution is unlimited.

STATISTICS FOR THE TWO-SAMPLE SURVIVAL ANALYSIS PROBLEM BASED ON PRODUCT LIMIT ESTIMATORS OF THE SURVIVAL FUNCTIONS

by

Margaret O'Sullivan

and

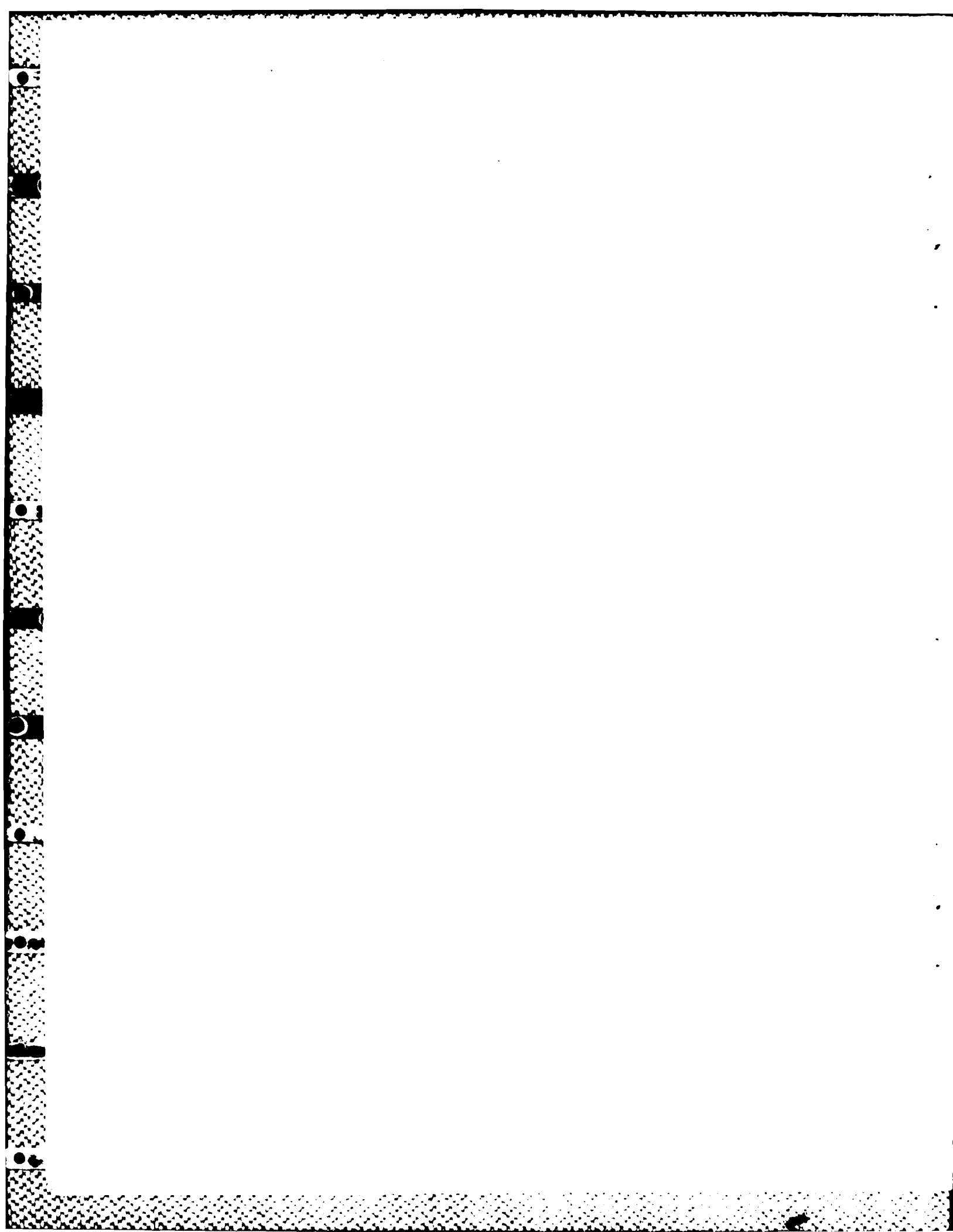
Thomas R. Fleming

FOR TECHNICAL INFORMATION REPORT
OFFICE OF STATISTICAL THEORY
This technical report has been reviewed and
approved for public release by AFOSR. The
copyright is unlimited.
DISTRIBUTION STATEMENT
This is Technical Information Report No. 163

Technical Report No. 163

November 1986

87-2 20 239



STATISTICS FOR THE TWO-SAMPLE SURVIVAL ANALYSIS PROBLEM
BASED ON PRODUCT LIMIT ESTIMATORS OF THE SURVIVAL FUNCTIONS

by

Margaret O'Sullivan
Center for Stochastic Processes
University of North Carolina
Chapel Hill, NC 27514

and

Thomas R. Fleming
Department of Biostatistics
University of Washington, SC-32
Seattle, WA 98195

Accession For	
1915 SPA&I	X
1917 TAP	
Unpublished	
Justification	
By	
Distribution/	
Availability Codes	
Dist	
A-1	



Summary

A class of statistics for the two-sample survival analysis problem is introduced. The SW-statistic may be written as the integral of a weighted difference in the estimated survival functions, the integral being with respect to Lebesgue measure on time. Since the integral is with respect to real-time the statistics are not generalized rank-statistics. However, with an appropriate choice of weight function they are non-parametric in the sense that weak convergence is guaranteed for any underlying configuration of survival and censoring distributions.

Asymptotic distribution theory under the null is derived. Consistency under a fixed alternative is shown. Efficacy expressions under natural sequences of local alternatives are given and an expression for the most efficient weight function is developed. The asymptotic efficiencies of some specific SW-statistics under the proportional hazards alternative are examined.

Research partially supported by the Air Force Office of Scientific Research Grant No. F49620 85 C 0144.

INTRODUCTION

Various nonparametric test procedures for the two-sample censored data survival analysis problem have been proposed. These include the weighted logrank tests (Gill 1980), their supremum versions (Fleming, Harrington and O'Sullivan 1986), a generalized Smirnov test (Fleming et al. 1980) as well as the orthogonal-score-statistics procedure of Breslow, Edler and Berger (1984). These procedures are based on generalized rank statistics and hence they are certainly robust. Indeed, because they are based on ranks they are invariant under monotone increasing transformations of the data. However, such invariance is not always a desirable feature (O'Sullivan 1986). A difference which is large may become negligible under a monotone increasing transformation of the data (Figure 1). Hence rank-statistics will not distinguish the two situations of Figure 1 in their powers and yet intuitively in applications one would expect a reasonable test procedure to detect the larger difference with more power than the smaller difference. A class of non-rank-based, nonparametric test procedures for this problem is proposed here. The test statistics reduce to the scaled difference of two generalized L-statistics in uncensored data. (The generalization allows random as well as deterministic weight functions in the usual definition of L-statistics).

The basic set-up and notation along with the SW-statistics themselves are introduced in section 1. Section 2 is concerned with asymptotic distribution theory for the numerator and consistency results for the denominator of the SW-statistic.

In section 3 these results are exploited to yield null distribution theory, consistency under a fixed alternative and an expression for the efficacy under a sequence of local alternatives. Finally, since these statistics are indexed by a set of weight functions, the choice of an efficient weight function is discussed in section 4.

1. DEFINITIONS AND ASSUMPTIONS

Let $\{(X_{ij}, U_{ij}); j = 1, \dots, n_i; i = 1, 2\}$ be $2n$ independent positive random variables where $n = n_1 + n_2$. For $i = 1$ and 2 , suppose X_{ij} and U_{ij} have (right continuous) survival functions $S_i(\cdot)$ and $C_i(\cdot)$ respectively. As is usual, X_{ij} , U_{ij} and $\tilde{X}_{ij} = \min(X_{ij}, U_{ij})$ will be termed the survival time, censoring time and observation time random variables respectively for individual j in group i . We wish to test the null hypothesis $H_0: S_1(\cdot) = S_2(\cdot)$ based on the data $\{\tilde{X}_{ij}, I[X_{ij} \leq U_{ij}]; j = 1, \dots, n_i; i = 1, 2\}$, where $I[A]$ denotes the indicator function of the set A . This is the simple two-sample censored data survival analysis problem under random censorship.

We will assume throughout that $S_i(\cdot)$ $i = 1, 2$ are continuous, (though not necessarily absolutely continuous). On the other hand we allow the $C_i(\cdot)$ $i = 1, 2$ to be arbitrary monotone decreasing functions on $[0, \infty)$ with $C_i(0) = 1$. Thus improper censoring distributions are allowed.

Let $\hat{S}_i(\cdot)$ and $\hat{C}_i(\cdot)$ denote the Kaplan-Meier estimators of the survival functions $S_i(\cdot)$ and $C_i(\cdot)$ respectively. Define

$T_c = \sup\{t: ((\hat{S}_1(t) \vee \hat{S}_2(t)) \wedge \hat{C}_1(t) \wedge \hat{C}_2(t)) > 0\}$ where $x \vee y$ denotes $\max(x, y)$ and $x \wedge y$ denotes $\min(x, y)$. Both S_1 and S_2 are 'well-estimated' on $[0, T_c]$ in the sense that for $i = 1$ and 2

$$E(\hat{S}_i(t)I[t \leq T_c]) = E(S_i(t)I[t \leq T_c]).$$

Thus $[0, T_c]$ is a natural interval on which to compare S_1 and S_2 .

The interval $[0, T_c]$ includes the interval $[0, T]$ where $T = T_1 \wedge T_2$ and $T_i = \sup\{t: (\hat{S}_i(t) \wedge \hat{C}_i(t)) > 0\}$. Only information on $[0, T]$ is used by the generalized rank procedures mentioned above. Since the generalized rank procedures in essence compare hazard functions, and hazard functions in both groups can only be estimated when the risk sets in both groups are non-empty (i.e. on $[0, T]$), then $[0, T]$ is the natural interval to use for these procedures. However, the interval $[0, T_c]$ is more appropriate for procedures which compare survival functions.

Let $\hat{W}(\cdot)$ be a random weight function, measurable with respect to $\sigma(\tilde{X}_{ij}, I(X_{ij} \leq U_{ij}); j = 1, \dots, n_i; i = 1, 2, \dots)$ where $\sigma(A)$ is the σ -algebra generated by A . ($\hat{W}(\cdot)$ estimates an underlying deterministic lebesgue measurable weight function $W(\cdot)$ in a sense to be defined shortly). We define a member of the SW-class of statistics to be

$$SW = \sqrt{\frac{n_1 n_2}{n_1 + n_2}} \int_0^{T_c} \hat{W}(u) (\hat{S}_1(u) - \hat{S}_2(u)) du.$$

We will propose test procedures for the two-sample censored data survival analysis problem which are based on these statistics. Note that by a simple integration by parts, SW can be written as

$$\sqrt{\frac{n_1 n_2}{n_1 + n_2}} \left[\int_0^{T_2} \left(\int_0^t \hat{W}(v) dv \right) d\hat{S}_2(t) - \int_0^{T_1} \left(\int_0^t \hat{W}(v) dv \right) d\hat{S}_1(t) \right]$$

in uncensored data, which is the difference of two L-statistics if \hat{W} is deterministic.

2. DISTRIBUTION THEORY FOR SW

Initially we will consider the component of SW from the i^{th} group

$$\sqrt{n_i} \int_0^{T_c} \hat{W}(u) (\hat{S}_i(u) - S_i(u)) du.$$

For ease of notation the subscript i will be dropped for now. We seek distribution theory not only under the null but also under a fixed alternative and under a sequence of local alternatives.

Thus we allow the configurations (S^n, C^n, W^n) to vary with n the sample size.

Let τ^n be the population parameter corresponding to T .

Thus

$$\tau^n = \sup\{t: S^n(t) \wedge C^n(t) > 0\}$$

and for some limiting survival functions $S(\cdot)$ and $C(\cdot)$

$$\tau = \sup\{t: S(t) \wedge C(t) > 0\}.$$

We require that

$$(A1) \quad \tau^n \leq \tau \quad \text{and} \quad \lim_{n \rightarrow \infty} \tau^n = \tau.$$

Indeed in most cases of practical interest $\tau^n = \tau \forall n$.

Convergence of the configurations is also required in the sense that for the survival functions $S(\cdot)$ and $C(\cdot)$, and the weight

function $W(\cdot)$,

$$(A2) \quad \begin{cases} \lim_{n \rightarrow \infty} \|W^n(t) - W(t)\|_{[0, \tau]} = 0 \\ \lim_{n \rightarrow \infty} S^n(t) = S(t) \quad \text{and} \quad \lim_{n \rightarrow \infty} C^n(t) = C(t) \quad \forall t \in [0, \tau] \end{cases}$$

Assumptions which are to remain in effect unless otherwise specified will be denoted by $(A\#)$ throughout the text, where $\#$ is an integer.

The following theorem, which is basic in the derivation of asymptotic distribution theory for SW, is a generalization of Theorem 2.1 of Gill (1983). The proof follows the steps of Gill's proof quite closely and hence will not be presented here. Instead the reader is referred to Appendix 2 of O'Sullivan (1986), wherein a detailed proof is given.

Theorem 2.1

Let h^n , $n = 1, 2, \dots$ and h be non-negative, non-increasing, continuous, bounded functions on $[0, \tau^n]$ $n = 1, 2, \dots$ and $[0, \tau]$ respectively. Assume that

$$\lim_{n \rightarrow \infty} h^n(t) = h(t) \quad 0 \leq t \leq \tau,$$

$$- \int_0^\tau \frac{(h(v))^2}{(S(v))^2(C(v))} dS(v) = \sigma^2 < \infty, \quad \text{and}$$

$$\lim_{n \rightarrow \infty} \sigma_n^2 = \lim_{n \rightarrow \infty} - \int_0^{\tau^n} \frac{(h^n(v))^2}{(S^n(v))^2(C^n(v))} dS^n(v) = \sigma^2.$$

If $Z^n(t) = -\sqrt{n} \frac{(\hat{S}(t) - S^n(t))}{S^n(t)}$ and $Z^\infty(t) = B \left(-\int_0^{t \wedge \tau} \frac{dS(v)}{(S(v))^2 (C(v))^{-1}} \right)$

for a standard Brownian motion B , then on $D[0, \infty]$

$$(h^n(t \wedge T) Z^n(t \wedge T)) \Rightarrow h(t \wedge \tau) Z^\infty(t \wedge \tau).$$

If also

$$\lim_{n \rightarrow \infty} \int_0^t |d(h^n(v) - h(v))| = 0 \quad \forall t < \tau$$

then on $D[0, \infty]$

$$\int_0^{t \wedge T} h^n(v) dZ^n(v) \Rightarrow \int_0^{t \wedge \tau} h(v) dZ^\infty(v)$$

and

$$(2.2) \quad \int_0^{t \wedge T} Z^n(v) dh^n(v) \Rightarrow \int_0^{t \wedge \tau} Z^\infty(v) dh(v)$$

where, by definition

$$\int_0^S h(v) dZ^\infty(v) = h(s) Z^\infty(s) - \int_0^S Z^\infty(v) dh(v) \quad \square$$

Conclusion (2.2) is most useful in determining asymptotic distribution theory for SW.

Corollary 2.3

Suppose

$$(2.4) \quad \lim_{n \rightarrow \infty} \int_0^{\tau^n} W^n(u) S^n(u) du = \int_0^\tau W(u) S(u) du < \infty$$

$$\begin{aligned}
 (2.5) \quad \lim_{n \rightarrow \infty} & - \int_0^{\tau^n} \frac{\left(\int_u^{\tau^n} |W^n(v)| S^n(v) dv \right)^2}{(S^n(u))^2 (C^n(u))^{-}} dS^n(u) \\
 & = - \int_0^{\tau} \frac{\left(\int_u^{\tau} |W(v)| S(v) dv \right)^2}{(S(u))^2 (C(u))^{-}} dS(u) < \infty
 \end{aligned}$$

then on $C[0, \infty]$

$$(2.6) \quad U^n(\cdot) = \sqrt{n} \int_0^{\cdot \wedge T} W^n(u) (\hat{S}(u) - S^n(u)) du \Rightarrow U^\infty(\cdot)$$

where $U^\infty(\cdot)$ is a mean zero Gaussian process with variance function

$$\sigma^2(t) = - \int_0^{t \wedge \tau} \frac{\left(\int_u^{t \wedge \tau} W(v) S(v) dv \right)^2}{(S(u))^2 (C(u))^{-}} dS(u)$$

Proof.

Let $h^n(u) = \int_u^{\tau^n} W^n(v) S^n(v) dv$ and $h(u) = \int_u^{\tau} W(v) S(v) dv$. Then $U^n(t) = \int_0^{t \wedge T} Z^n(u) dh^n(u)$. If the weight function $W^n(\cdot)$ is positive then the conclusion follows from (2.2) of Theorem 2.1, with $U^\infty(t) = \int_0^{t \wedge \tau} Z^\infty(u) W(u) S(u) du$. The result also holds, if $W^n(\cdot)$ is not necessarily positive as is shown in Theorem 2.3.1 of O'Sullivan (1986).

We now introduce the time-point τ_c . If $\tau_i \leq \tau_{i'}$, $i, i' = 1$ or 2 , $i \neq i'$, define

$$\tau_c = \begin{cases} \tau_i, & \text{if } S_i(\tau_i) = 0 \text{ and } C_i^-(\tau_i) > 0 \\ \tau_i & \text{otherwise} \end{cases}$$

In almost all cases by Lemma A.1 τ_c is the limiting form of T_c in that $T_c \xrightarrow{P} \tau_c$. Indeed in general $T \wedge T_c \wedge \tau_c \xrightarrow{P} \tau \wedge \tau_c$. Since $U^n(\cdot)$ is tight in $C[0, \infty]$, Theorem 4.2 of Billingsley (1968) allows replacement of (2.6) with

$$\sqrt{n} \int_0^{\tau \wedge T_c \wedge \tau_c} W^n(u) (\hat{S}(u) - S^n(u)) du \Rightarrow U^\infty(\cdot \wedge \tau_c).$$

For the remainder of this paper, unless otherwise specified we assume that

$$(A3) \quad \tau < \infty \quad \text{and} \quad \|W(\cdot)\|_{[0, \tau]} < \infty$$

where $\|\cdot\|_A$ is the supremum norm over the set A . Certainly the condition that $\tau < \infty$ is always true in practice. The techniques used in this paper are heavily dependent on the boundedness of $W(\cdot)$ and further work will be necessary to generalize the results to include random weight functions in SW which are unbounded in the limit. Note however that Corollary 2.3 which deals with deterministic weight functions is general enough to allow unbounded deterministic weight functions.

Now we replace the deterministic weight function $W^n(\cdot)$ with its estimator $\hat{W}(\cdot)$ a random weight function. Suppose

$$(A4) \quad \|\hat{W}(\cdot) - W(\cdot)\|_{[0, T_c \wedge \tau_c]} \xrightarrow{P} 0 \quad n \rightarrow \infty$$

Lemma 2.7

If

$$(2.8) \quad \left\| \frac{\hat{W}(u) - W^n(u)}{\sqrt{(C^n(u))^{-1}}} \right\|_{[0, \tau \wedge T_c \wedge \tau_c]} \xrightarrow{P} 0$$

then

$$\int_0^{\tau} \sqrt{C(u)}^{-1} (\hat{W}(u) - W^n(u)) (\hat{S}(u) - S^n(u)) du \xrightarrow{P} 0$$

Proof

It is enough to show that

$\sqrt{n} \sqrt{C^n(u)}^{-1} (\hat{S}(u) - S^n(u)) \mid \mid_{[0, \tau]}$ is bounded in probability (henceforth denoted by BP). Let $h^n(v) = S^n(v) \sqrt{C^n(v)}^{-1}$ and $h(v) = S(v) \sqrt{C(v)}^{-1}$. Then

$$- \int_0^{\tau} \frac{(h(v))^2}{(S(v))^2 C(v)} dS(v) = 1 - S(\tau) < \infty, \text{ and}$$

$$- \lim_{n \rightarrow \infty} \int_0^{\tau^n} \frac{h^n(v)}{(S^n(v))^2 C^n(v)} dS^n(v) = \lim_{n \rightarrow \infty} (1 - S^n(\tau^n)) = 1 - S(\tau).$$

Thus the conditions of Theorem 2.1 which guarantee convergence of $h^n(\cdot \wedge T) Z^n(\cdot \wedge T)$ are satisfied, except that h and h^n are not necessarily continuous but rather are left continuous. Lemma 2.A.6 of O'Sullivan (1986) shows that under these conditions $h^n(\cdot \wedge T) Z^n(\cdot \wedge T)$ is stable (or 'tight') at the end-point τ , even if h and h^n are only left continuous. That is to say, given $\delta > 0$ and $\epsilon > 0 \exists t^* < \tau$ and n^* such that $\forall n \geq n^*$

$$P[\mid \mid \sqrt{n} \sqrt{C^n(\cdot)}^{-1} (\hat{S}(\cdot) - S^n(\cdot)) \mid \mid_{[t^*, \tau]} > \epsilon] < \delta.$$

$\mid \mid \sqrt{n} (\hat{S}(u) - S^n(u)) \mid \mid_{[0, t^*]}$ is BP as a consequence of Theorem 2.1. Thus $\mid \mid \sqrt{n} \sqrt{C^n(\cdot)}^{-1} (\hat{S}(\cdot) - S^n(\cdot)) \mid \mid_{[0, \tau]}$ is B.P. as required.

The conditions on $\hat{W}(\cdot)$ implied by (2.4), (2.5) and (2.8) certainly guarantee the desired weak convergence. However more direct and interpretable conditions on $\hat{W}(\cdot)$ are desirable to facilitate the generation of SW statistics which are stable asymptotically. We seek conditions on $\hat{W}(\cdot)$ which will yield SW

asymptotically stable for all choices of underlying survival and censoring configurations $(S^n(\cdot), C^n(\cdot))$. In this sense the proposed tests will be non-parametric.

Definition

For two sequences of stochastic processes $X^n(\cdot)$ and $Y^n(\cdot)$ defined on $[0, \infty)$, by $X^n(\cdot) = O(Y^n(\cdot))$ we mean that \exists a constant Γ such that, given $\epsilon > 0$ \exists an integer n_0 with

$$P[|X^n(t)| \leq \Gamma |Y^n(t)| \quad \forall t \geq 0, \quad \forall n \geq n_0] \geq 1 - \epsilon$$

Note that if $X^n(\cdot)$ and $Y^n(\cdot)$ are deterministic functions, then the above definition reduces to the existence of a constant Γ such that $|X^n(t)| \leq \Gamma |Y^n(t)| \quad \forall t \geq 0, \quad \forall n$.

Theorem 2.9

Suppose

$$W^n(\cdot) = O(((C^n(\cdot) \wedge \tau^n))^{-1/2}), \text{ then on } C[0, \infty]$$

$$\sqrt{n} \int_0^{T_c \wedge T} W^n(u) (\hat{S}(u) - S^n(u)) du \Rightarrow U^\infty(t)$$

Under the stronger condition that

(A5) $\exists \delta > 0$ with

$$W^n(\cdot) = O(((C^n(\cdot) \wedge \tau^n))^{-1/2+\delta})$$

and

$$\dot{W}(\cdot) = O((\dot{C}^-(\cdot))^{-1/2+\delta}),$$

then

$$\sqrt{n} \int_0^{T_c \wedge T} \dot{W}(u) (\hat{S}(u) - S^n(u)) du \xrightarrow{P} 0.$$

Proof

By (A3), (2.4) is satisfied. For some constant Γ ,

$$\begin{aligned} - \int_0^\tau \frac{\left(\int_u^\tau |W(v)| S(v) dv \right)^2}{(S(u))^2 (C(u))^-} dS(u) &\leq -\Gamma^2 \int_0^\tau \frac{\left(\int_u^\tau S(v) dv \right)^2}{(S(v))^2} dS(v) \\ &= \Gamma^2 \sigma^2(S(\cdot)I[0 \leq \cdot < \tau]) < \infty \end{aligned}$$

where $\sigma^2(S(\cdot)I[0 \leq \cdot < \tau])$ denotes the variance calculated from the survival function $S(\cdot)I[0 \leq \cdot < \tau]$ and the equality follows from Lemma A.2 of the appendix. Define

$$\begin{aligned} g(u) &= \frac{\left(\int_u^\tau |W(v)| S(v) dv \right)^2}{(S(u))^2 (C(u))^-} I[0 \leq u < \tau] \\ g^n(u) &= \frac{\left(\int_u^{\tau^n} |W^n(v)| S^n(v) dv \right)^2}{(S^n(u))^2 (C^n(u))^-} I[0 \leq u < \tau^n]. \end{aligned}$$

Also let $Y_n = X_n I[0 \leq X_n < \tau^n]$ and $Y = XI[0 \leq X < \tau]$ where X_n and X have survival functions $S^n(\cdot)$ and $S(\cdot)$ respectively. The survival functions for Y_n and Y are $(S^n(t) - S^n(\tau^n))$ and $(S(t) - S(\tau))$ for $t > 0$ respectively. Since $Y_n \xrightarrow{d} Y$, g is continuous at 0, g has at most a countable number of discontinuities on $(0, \infty)$ and $S(\cdot)$ is continuous on $(0, \infty)$, then $g(Y_n) \xrightarrow{d} g(Y)$. Given $\epsilon > 0$ $\exists n_0$ and $t_0 < \tau$ such that $\forall n \geq n_0$, $P[Y_n \leq t_0] > 1 - \epsilon$. Also, $\lim_{n \rightarrow \infty} \|g^n(x) - g(x)\|_{[t_0, t_1]} = 0$. Hence $g^n(Y_n) - g(Y_n) \xrightarrow{p} 0$ and so $g^n(Y_n) \xrightarrow{d} g(Y)$. Boundedness of $g^n(Y_n)$ uniformly in n yields $\lim_{n \rightarrow \infty} E(g^n(Y_n)) = E(g(Y))$ and hence (2.5).

Finally we need to verify that the stronger condition (A5) yields (2.3). (2.8) is a trivial consequence of (A4) unless

$C^-(\tau \wedge \tau_c) = 0$, in which case we note that $\tau = \tau_c$. Thus suppose $C^-(\tau) = 0$ and $\tau = \tau_c$. Given $\epsilon > 0$ $\exists t_0 < \tau$ such that $0 < (C^-(t_0))^\delta < \epsilon/2$.

$$\left\| \frac{\hat{W}(u) - W^n(u)}{\sqrt{C^n(u)}} \right\|_{[0, \tau \wedge \tau_c]} \leq \left\| \frac{\hat{W}(u) - W^n(u)}{\sqrt{C^n(u)}} \right\|_{[0, t_0 \wedge \tau \wedge \tau_c]} + \left\| \frac{\hat{W}(u) - W^n(u)}{\sqrt{C^n(u)}} \right\|_{[t_0, \tau \wedge \tau_c]}$$

The first term on the right hand side converges to 0 in probability as a consequence of (A4). For the second term \exists constants Γ_1 and Γ_2 such that

$$\begin{aligned} & \left\| \frac{\hat{W}(u) - W^n(u)}{\sqrt{C^n(u)}} \right\|_{[t_0, \tau \wedge \tau_c]} \\ & \leq \Gamma_2 \left\| \frac{\hat{C}^-(u)}{(C^n(u))^\gamma} \right\|_{[t_0, \tau]} (\hat{C}^-(t_0))^\delta + \Gamma_1 ((C^n(t_0))^\gamma)^\delta \\ & \leq \Gamma_2 \sqrt{\epsilon} + \Gamma_1 \epsilon \end{aligned}$$

with probability at least $1 - 3\epsilon$ if n is large enough, using Theorem 3.2.1 of Gill (1980) for the first component. Thus

$$\left\| \frac{\hat{W}(u) - W^n(u)}{\sqrt{C^n(u)}} \right\|_{[t_0, \tau \wedge \tau_c]} \xrightarrow{P} 0.$$

The final step in the derivation of asymptotic distribution theory is to show that the contribution to SW over $(T \wedge T_c \wedge \tau_c, T_c)$ is asymptotically negligible.

$$\sqrt{n} \int_{T \wedge T_c \wedge \tau_c}^{T_c} \hat{W}(u) (\hat{S}(u) - S^n(u)) du = \sqrt{n} \int_{T \wedge T_c \wedge \tau_c}^{\tau \wedge T_c} \hat{W}(u) (\hat{S}(u) - S^n(u)) du$$

$$+ \bar{n} \int_{\tau^n \wedge T_c}^{T_c} \hat{W}(u) (\hat{S}(u) - S^n(u)) du.$$

We will treat these two components separately.

Lemma 2.10

If

(A6) $\bar{n}(T - \tau^n)$ is BP, then

$$\bar{n} \int_{T \wedge T_c \wedge \tau_c}^{\tau^n \wedge T_c} \hat{W}(u) (\hat{S}(u) - S^n(u)) du \xrightarrow{P} 0$$

Proof.

For some constant Γ with high probability

$$\begin{aligned} & \bar{n} \int_{T \wedge T_c \wedge \tau_c}^{\tau^n \wedge T_c} \hat{W}(u) (\hat{S}(u) - S^n(u)) du \\ & \leq \Gamma \| \hat{S}(u) - S^n(u) \|_{[0, \tau]} | \bar{n}(\tau^n - T) | \text{ and} \end{aligned}$$

$\hat{S}(u) - S^n(u) \|_{[0, \tau]} \xrightarrow{P} 0$ by Gill (1980) Theorem 4.1.1. \square

Remark. The uniform consistency of $\hat{S}(\cdot)$ on $[0, \tau]$ is stated but not proved in the reference cited above. A slight modification of the proof of Theorem 1, page 304, Shorack and Wellner (1986) yields the result. An alternative proof may be obtained from the author and will be included in a forthcoming monograph by Fleming, T.R. and Harrington, D.P. Condition (A6) holds very generally at least under a fixed configuration, as is shown in O'Sullivan (1986) using some results from extreme-value

Lemma 2.11

(A7) If $\tau_1 = \tau_2$, assume that $\bar{n}(\tau_1^n - \tau_2^n)$ is bounded, then

$$\frac{1}{n} \int_{\tau^n \wedge T_c}^{T_c} \hat{W}(u) (\hat{S}(u) - S^n(u)) du \xrightarrow{P} 0$$

Proof.

$$(2.12) \quad \frac{1}{n} \int_{\tau^n \wedge T_c}^{T_c} \hat{W}(u) (\hat{S}(u) - S^n(u)) du = - \frac{1}{n} \int_{\tau^n \wedge T_c}^{T_c} \hat{W}(u) S^n(u) du.$$

Under a fixed configuration, either $S(\tau)=0$ so that (2.12) is identically zero, or $S(\tau)>0$. In this case

$\lim_{n \rightarrow \infty} P[\hat{S}(T) = 0] = 0$, $\lim_{n \rightarrow \infty} P[\hat{C}(T) = 0] = 1$ and $\lim_{n \rightarrow \infty} P[T_c > \tau] = 0$ so the result holds.

Under a sequence of local configurations, if $\tau_i < \tau_{3-i}$ for $i = 1$ or 2 , then $S(\tau_i) > 0$ and $T_c \xrightarrow{P} \tau_c = \tau_i$ by Lemma A.1. Hence $\lim_{n \rightarrow \infty} P[T_c = T_i \leq \tau_1^n \wedge \tau_2^n] = 1$ and the result holds. If $\tau_1 = \tau_2 = \tau$ it is enough to consider $\tau^n < \tau \forall n$.

$$\left| \frac{1}{n} \int_{\tau^n \wedge T_c}^{T_c} \hat{W}(u) S^n(u) du \right| \leq \frac{1}{n} (\tau_1^n - \tau_2^n) S^n(\tau^n) \|\hat{W}(u)\|_{(\tau^n, T_c)}.$$

If $S(\tau) = 0$ then the result is proven. Otherwise $S(\tau) > 0$ and $C^n(\tau^n) = 0$ for n large enough. In this case $\hat{C}(\tau^n) \xrightarrow{P} 0$ since $\|\hat{C}(u) - C^n(u)\|_{[0, \tau]} \xrightarrow{P} 0$, and $\|\hat{W}(u)\|_{[\tau^n, T_c]} \xrightarrow{P} 0$. \square

We are finally in a position to give asymptotic distribution theory for SW. The natural condition

$$(A8) \quad \lim_{n \rightarrow \infty} \frac{n_i}{n} = \rho_i > 0$$

is imposed. Note, that the assumptions listed so far were given without regard to a group subscript i . We assume that the conditions hold for both groups $i = 1, 2$.

Lemma 2.13

$$\sqrt{\frac{n_1 n_2}{n_1 + n_2}} \int_0^{T_c} (\hat{W}(\hat{S}_1 - \hat{S}_2) - \hat{W}(S_1^n - S_2^n)) du \xrightarrow{d} N(0, \sigma_{SW}^2)$$

$$\text{where } \sigma_{SW}^2 = - \sum_{i=1}^2 \rho_{3-i} \int_0^{\tau_i} \frac{\left(\int_u^{\tau_i} W(v) S(v) dv \right)^2}{(S_i(u))^2 (C_i(u))} dS_i(u).$$

Proof.

By Theorem 2.9 and independence

$$\sqrt{\frac{n_1 n_2}{n_1 + n_2}} \left\{ \int_0^{T_1 \wedge T_c} W^n(u) (\hat{S}_1(u) - S_1^n(u)) du - \int_0^{T_2 \wedge T_c} W^n(u) (\hat{S}_2(u) - S_2^n(u)) du \right\}$$

$$\Rightarrow \sqrt{\rho_2} U_1^\infty(t) + \sqrt{\rho_1} U_2^\infty(t) \text{ on } C[0, \infty].$$

That $T_c \wedge \tau_c \rightarrow \tau_c$, the sequence is tight in $C[0, \infty]$ and Theorem 4.2 of Billingsley 1968 together imply

$$\sqrt{\frac{n_1 n_2}{n_1 + n_2}} \left(\int_0^{T_1 \wedge T_c \wedge \tau_c} W^n(u) (\hat{S}_1(u) - S_1^n(u)) du - \int_0^{T_2 \wedge T_c \wedge \tau_c} W^n(u) (\hat{S}_2(u) - S_2^n(u)) du \right)$$

$$\xrightarrow{d} \sqrt{\rho_2} \tilde{U}_1(\tau_c) + \sqrt{\rho_1} \tilde{U}_2(\tau_c)$$

$$= \sqrt{\rho_2} \tilde{U}_1(\tau_1) + \sqrt{\rho_1} \tilde{U}_2(\tau_2).$$

Theorem 2.9, Lemma 2.10 and Lemma 2.11 then yield the required result.

Having established the asymptotic behaviour of the numerator the next task is to propose consistent estimators of

σ_{sw}^2 . Let

$$\hat{\sigma}_{up}^2 = - \sum_{i=1}^2 \hat{\rho}_{3-i} \frac{n_i}{n_i - 1} \int_0^{T_i} \frac{\left(\int_u^{T_i} \hat{W}(v) \hat{S}_i(v) dv \right)^2}{\hat{S}_i(u) \hat{S}_i^-(u) \hat{C}_i^-(u)} d\hat{S}_i(u).$$

where $\hat{\rho}_i = n_i/n$. $\hat{\sigma}_{up}^2$ is termed the unpooled variance estimator. In uncensored data with $\hat{W}(\cdot) = 1$, $\int_0^{T_i} \hat{W}(u) \hat{S}_i(u) du = \bar{X}_i$, the sample mean from the i^{th} group and Lemma A.2 yields

$$- \frac{n_i}{n_i - 1} \int_0^{T_i} \frac{\left(\int_u^{T_i} \hat{W}(v) \hat{S}_i(v) dv \right)^2}{\hat{S}_i(u) \hat{S}_i^-(u) \hat{C}_i^-(u)} d\hat{S}_i(v) = \sum_{j=1}^{n_i} \frac{(X_{ij} - \bar{X}_i)^2}{n_i - 1},$$

the usual sample variance of survival times in the i^{th} group.

Thus $\hat{\sigma}_{up}^2$ is the natural estimator of the variance of SW at least in this classical case.

Under the null hypothesis it is tempting to substitute \hat{S}_p , the Kaplan-Meier estimator calculated using the two samples pooled, for \hat{S}_i in $\hat{\sigma}_{up}^2$. The resulting

$$\hat{\sigma}_p^2 = - \frac{n}{n - 1} \sum_{i=1}^2 \hat{\rho}_{3-i} \int_0^{T_c} \frac{\left(\int_u^{T_c} \hat{W}(v) \hat{S}_p(v) dv \right)^2}{\hat{S}_p(u) \hat{S}_p^-(u) \hat{C}_i^-(u)} d\hat{S}_p(u)$$

is termed the pooled variance estimator. Indeed simulation results suggest that $\hat{\sigma}_p^2$ is a better standardization factor for SW than $\hat{\sigma}_{up}^2$ under the null in many cases in small sample. We defer discussion of small sample properties to another paper however.

Theorem 2.14

$$(i) \quad \hat{\sigma}_{up}^2 \xrightarrow{p} \sigma_{sw}^2$$

Under H_0 : $S_1^n = S_2^n = S \quad \forall n$

$$(ii) \quad \hat{\sigma}_p^2 \xrightarrow{p} \sigma_{SW}^2$$

The proof of Theorem 2.14 is somewhat technical and is given in O'Sullivan (1986). Consistency of $\hat{\sigma}_p^2$ is proven only under the null hypothesis since general results on the consistency of the Kaplan-Meier estimator are known only under the random censorship model. Unless the survival distributions in the two groups are equal or the censoring distributions in the two groups are equal then the random censorship model does not hold in the pooled sample. Consistency of the Kaplan-Meier is basic in deriving consistency of the variance estimators. Thus, consistency of $\hat{\sigma}_p^2$ is not proven in general but is shown only under the null. Although consistency can also be shown for arbitrary configurations under the assumption of equal censoring distributions ($C_1^n = C_2^n \quad \forall n$), this assumption is very restrictive and we do not consider it to be an important case.

3. NULL THEORY, CONSISTENCY AND EFFICACIES

The purpose of this section is to summarize the results of Section 3 as they pertain to null distribution theory, consistency and asymptotic behaviour under a sequence of local alternatives. The following assumptions are made, for $i = 1$ and 2

$$(A1) \quad \tau_i^n \leq \tau_i \quad \forall n, \quad \lim_{n \rightarrow \infty} \tau_i^n = \tau_i, \quad ,$$

$$(A2) \quad \lim_{n \rightarrow \infty} \|W^n(u) - W(u)\|_{[0, \tau_i]} = 0,$$

$$\lim_{n \rightarrow \infty} S_i^n(t) = S_i(t) \text{ and } \lim_{n \rightarrow \infty} C_i^n(t) = C_i(t) \quad \forall t \in [0, \tau_i],$$

$$(A3) \quad \tau_i < \infty, \quad \|W(u)\|_{[0, \tau_i]} < \infty,$$

$$(A4) \quad \|\hat{W}(u) - W(u)\|_{[0, \tau_c \wedge \tau_i]} \xrightarrow{P} 0,$$

$$(A5) \quad \exists \delta > 0 \text{ such that}$$

$$W^n(\cdot) = O((C_i^n(\cdot \wedge \tau_i))^{.5+\delta})$$

and

$$\hat{W}(\cdot) = O((\hat{C}_i(\cdot))^{(.5+\delta)}),$$

$$(A6) \quad \sqrt{n} (T_i - \tau_i^n) \text{ is bounded in probability},$$

$$(A7) \quad \text{If } \tau_1 = \tau_2 \text{ then } \sqrt{n} (\tau_1^n - \tau_2^n) \text{ is bounded}$$

$$(A8) \quad \lim_{n \rightarrow \infty} \frac{n_1}{n_1 + n_2} = \rho_1 > 0.$$

Under a fixed configuration (A1), (A2) and (A7) are redundant, and (A6) holds except in pathological cases. In practice $\tau_i < \infty$ and (A5) implies that $W(\cdot)$ is bounded. (A8) also holds in general since the design of the experiment will usually ensure that (n_1/n) is a fixed positive fraction. Thus, only (A4) and (A5) need be of real concern for the purposes of null distribution theory and for consistency.

For a sequence of local alternatives it is most natural

to consider the censoring distributions as fixed and the alternatives are specified in terms of the convergent sequences of survival functions. In most cases of practical interest for $i=1$ and 2 , $C_i(\tau_i) = 0$ and $S_i(\tau_i) > 0$, i.e. there is a positive probability of surviving past the end of the study. Thus even under a sequence of configurations (A1) and (A7) are redundant in most cases of interest since $\tau_i^n = \tau_i \forall n$, $i = 1$ and 2 . As discussed above for a fixed configuration (A3) and (A8) are generally satisfied in practice. Thus for a sequence of local alternatives only (A2), (A4), (A5) and (A6) are of any real concern in general.

Let $SW^{UP} = SW / \sqrt{\sigma_{UP}^2}$ and $SW^P = SW / \sqrt{\sigma_P^2}$

Theorem 3.1

(i) Under the null hypothesis

$$SW^{UP} \xrightarrow{d} N(0,1), \text{ and } SW^P \xrightarrow{d} N(0,1).$$

(ii) A two-sided test based on SW^{UP} or SW^P is consistent against any fixed alternative such that $\left| \int_0^{\tau_c} W(u) (S_1(u) - S_2(u)) du \right| > 0$

(iii) If under a sequence of local alternatives, for some bounded function $D(\cdot)$ on $[0, \tau_c)$,

$$\sqrt{\frac{n_1 n_2}{n_1 + n_2}} (S_1^n(u) - S_2^n(u)) \rightarrow D(u)$$

uniformly on $[0, \tau_c)$, then

$$SW^{up} \xrightarrow{d} N \left(\frac{\int_0^{\tau_c} W(u) D(u) du}{\sqrt{\sigma_{SW}^2}}, 1 \right)$$

Proof

(i) This is a trivial consequence of Lemma 2.13 and Theorem 2.14

(ii) $\hat{\sigma}_{up}^2 \xrightarrow{p} \sigma_{SW}^2 < \infty$ so that $\hat{\sigma}_{up}^2$ is BP. Also,

$$\begin{aligned} \hat{\sigma}_p^2 &= - \int_0^{\tau_c} \frac{\left(\int_u^{\tau_c} \hat{W}(v) \hat{S}_p(v) dv \right)^2}{\hat{S}_p(u) \hat{S}_p(u)} \left(\frac{\hat{\rho}_2}{\hat{C}_1^-(u)} + \frac{\hat{\rho}_1}{\hat{C}_2^-(u)} \right) d\hat{S}_p(u) \\ &\leq -\Gamma \int_0^{\tau_c} \frac{\left(\int_u^{\tau_c} \hat{S}_p(v) dv \right)^2}{\hat{S}_p(u) \hat{S}_p(u)} d\hat{S}_p(u) \quad \text{for some constant} \end{aligned}$$

Γ with probability at least $1 - \epsilon \forall n \leq n_{\epsilon}$,

$$\leq (\tau_1 \vee \tau_2)^2 < \infty$$

Thus it remains to show that $|SW| \xrightarrow{p} \infty$.

$$\begin{aligned} &\left| \int_0^{\tau_c} \hat{W}(u) (S_1(u) - S_2(u)) du - \int_0^{\tau_c} W(u) (S_1(u) - S_2(u)) du \right| \\ &\leq \left| \int_0^{\tau_c \wedge T_c} (\hat{W}(u) - W(u)) (S_1(u) - S_2(u)) du \right| + \left| \int_{T_c \wedge \tau_c}^{\tau_c} \hat{W}(u) (S_1(u) - S_2(u)) du \right| \\ &\quad + \left| \int_{T_c \wedge \tau_c}^{\tau_c} W(u) (S_1(u) - S_2(u)) du \right|. \end{aligned}$$

The first term converges in probability to zero by (A3) and (A4).

Lemma A.1 and boundedness of $W(\cdot)$ prove that the last term converges to zero in probability. Similarly since $T_c \xrightarrow{p} \tau_c$ unless $\tau_1 < \tau_{3-i}$ with $S_i(\tau_1) = 0$ and $C_i^-(\tau_1) = 0$ (Lemma A.1), then the

second term also is asymptotically negligible except perhaps in this special case. In this special case, (taking $i=1$ without loss of generality),

$$\left| \int_{T_c \wedge \tau_c}^{T_c} \hat{W}(u) (S_1(u) - S_2(u)) du \right| = \left| \int_{\tau_1}^{T_c} \hat{W}(u) S_2(u) du \right|$$

$$\leq \Gamma(\hat{C}_1(\tau_1))^{.5+\delta} |T_c - \tau_1| \text{ for some constant } \Gamma,$$

$$\xrightarrow{P} 0$$

by consistency of $\hat{C}_1(\tau_1)$ for $C_1(\tau_1)$. Thus

$$\left| \frac{n_1 + n_2}{\sqrt{n_1 n_2}} SW \right| \xrightarrow{P} \left| \int_0^{\tau_c} W(u) (S_1(u) - S_2(u)) du \right| > 0$$

and hence $|SW| \xrightarrow{P} \infty$

(iii) By Lemma 2.13 and Theorem 2.14 it is enough to show that

$$\frac{n_1 n_2}{\sqrt{n_1 + n_2}} \int_0^{T_c} \hat{W}(u) (S_1^n(u) - S_2^n(u)) du \xrightarrow{P} \int_0^{\tau_c} W(u) D(u) du$$

Now,

$$\frac{n_1 n_2}{\sqrt{n_1 + n_2}} \int_0^{T_c} \hat{W}(u) (S_1^n(u) - S_2^n(u)) du - \int_0^{\tau_c} W(u) D(u) du.$$

$$\stackrel{a}{=} \frac{n_1 n_2}{\sqrt{n_1 + n_2}} \int_0^{T_c \wedge \tau_c} \hat{W}(u) (S_1^n(u) - S_2^n(u)) du - \int_0^{\tau_c} W(u) D(u) du,$$

because $p[T_c > \tau_c] \xrightarrow{P} 0$. To see this note that under a sequence of local alternatives $T_c > \tau_c$ can only happen if $\tau_i < \tau_{3-i}$, for $i=1$ or 2 , with $C_i(\tau_i) = 0$ and $S(\tau_i) > 0$, in which case

$$p[\hat{C}_1(\tau_1) = 0] \xrightarrow{P} 1.$$

$$\frac{\sqrt{n_1 n_2}}{\sqrt{n_1 + n_2}} \int_0^{T_c \wedge \tau_c} (\hat{W}(u) - W(u)) (S_1^n(u) - S_2^n(u)) du \xrightarrow{P} 0$$

since $\frac{\sqrt{n_1 n_2}}{\sqrt{n_1 + n_2}} \|S_1^n(u) - S_2^n(u)\|_{[0, \tau_c]}$ is bounded and (A4)

holds. Thus (4.2) is asymptotically equivalent to

$$\frac{\sqrt{n_1 n_2}}{\sqrt{n_1 + n_2}} \int_0^{T_c \wedge \tau_c} W(u) (S_1^n(u) - S_2^n(u)) du - \int_0^{\tau_c} W(u) D(u) du.$$

$$a = - \int_{T_c \wedge \tau_c}^{\tau_c} W(u) D(u) du \xrightarrow{P} 0$$

$$\left(\int_0^{\tau_c} W(u) D(u) du \right)^2$$

Note that $e(SW^{UP}) = \frac{\left(\int_0^{\tau_c} W(u) D(u) du \right)^2}{\sigma_{SW}^2}$ is termed the efficacy of

SW^{UP} under the sequence of alternatives specified by $D(\cdot)$.

4. EFFICIENT WEIGHT FUNCTIONS

The objective in this section is to find a weight function $W_{opt}(\cdot)$ which maximizes $e(SW^{UP})$ over all possible weight functions $W(\cdot)$ for a fixed $S(\cdot)$, $C_1(\cdot)$ and $C_2(\cdot)$ and for local alternatives specified by $D(\cdot)$. Since $e(SW^{UP})$ is invariant under scalar multiplication of $W(\cdot)$ the constraint is imposed

$$(4.1) \quad 1 = \sigma_{sw}^2 = - \int_0^{\tau_c} \frac{\left(\int_u^{\tau_c} W(v) S(v) dv \right)^2}{S(u) S^{-}(u)} \left(\frac{\rho_2}{C_1^{-}(u)} + \frac{\rho_1}{C_2^{-}(u)} \right) dS(u).$$

Direct maximization of $\left(\int_0^{\tau_c} W(u) D(u) du \right)^2$ with respect to $W(\cdot)$

subject to $\sigma_{sw}^2 = 1$ is a difficult problem in calculus of variations and indeed the Euler-Lagrange equations are in general not solvable. An alternative approach is to transform the problem to the maximization of $e(SW^{up})$ with respect to $h(\cdot) = \int_0^{\tau_c} W(u) S(u) du$, subject to the additional constraint that $h(\tau_c) = 0$. Some regularity will be required. The optimal $h(\cdot)$ is denoted by $h_{opt}(\cdot)$.

Lemma 4.2

If $\lim_{u \uparrow \tau_c} \frac{D(u)}{S(u)} < \infty$, $S(\cdot)$ and $D(\cdot)$ are differentiable and

$\frac{d}{du} S(u) \neq 0 \quad \forall u \in [0, \tau_c]$, then

$$h_{opt}(u) = \frac{S^2(u) C_1^{-}(u) C_2^{-}(u)}{\rho_1 C_1^{-}(u) + \rho_2 C_2^{-}(u)} \frac{\frac{d}{du} \left(\frac{D(u)}{S(u)} \right)}{\frac{d}{du} (S(u))}, \quad u < \tau_c,$$

$$h_{opt}(\tau_c) = 0.$$

Proof

Let $V(u) = D(u)/S(u)$. Since $D(0) = 0$, $V(0) = 0$ and integration by parts yields

$$\int_0^{\tau_c} W(u) D(u) du = - \int_0^{\tau_c} V(u) dh(u) = \int_0^{\tau_c} h(u) V'(u) du$$

where $V'(u) = \frac{d}{du} (V(u))$. Let $A(u) = - \frac{d}{du} \left((S(u)) \frac{\rho_1 \bar{C}_1(u) + \rho_2 \bar{C}_2(u)}{S^2(u) \bar{C}_1(u) \bar{C}_2(u)} \right)$.

Then

$$\begin{aligned} \left(\int_0^{\tau_c} W(u) D(u) du \right)^2 &= \left(\int_0^{\tau_c} \frac{V'(u)}{A(u)} A(u) h(u) du \right)^2 \\ &\leq \left(\int_0^{\tau_c} \frac{(V'(u))^2}{A(u)} du \right) \left(\int_0^{\tau_c} A(u) h^2(u) du \right) \\ &= \int_0^{\tau_c} \frac{(V'(u))^2}{A(u)} du \end{aligned}$$

where the first inequality is an application of the Cauchy-Schwartz inequality and the second equality follows from the constraint (4.1). The inequality is an equality if and only if

$$\frac{V'(u)}{A(u)} = \sqrt{A(u)} h(u), \quad u \in [0, \tau_c].$$

If $\lim_{u \uparrow \tau_c} h_{opt}(u) \neq 0$ then the solution requires h_{opt} to

have a mass point at τ_c . If censoring is continuous at τ_c or $S(\tau_c) = 0$ then certainly $\lim_{u \uparrow \tau_c} h_{opt}(u) = 0$ if $V'(u)$ is bounded on some $(\tau_c - \epsilon, \tau_c)$, $\epsilon > 0$. However if h_{opt} is not continuous at τ_c then an optimal weight function $W(\cdot)$ will not exist. Under the assumption that $h_{opt}(\cdot)$ is differentiable then the optimal weight function W_{opt} which maximizes $e(SW)$ is given by

$$W_{opt}(t) \propto \frac{1}{S(t)} \frac{d}{dt} \left(\frac{S^2(t) C_1^{-}(t) C_2^{-}(t)}{\rho_1 C_1^{-}(t) + \rho_2 C_2^{-}(t)} \right) \frac{\frac{d}{dt} (D(t)/S(t))}{\frac{d}{dt} S(t)}$$

Even if an optimal weight function exists, $W_{opt}(\cdot)$ need not satisfy the regularity conditions of section 3. For example, $W_{opt}(\cdot)$ need be bounded on $[0, \tau_c)$. However it is clear from Corollary 2.3 that the weaker conditions (2.4) and (2.5) will yield weak convergence for

$$\frac{1}{\sqrt{\sigma_{SW}^2}} \sqrt{\frac{n_1 n_2}{n_1 + n_2}} \int_0^{T_1 \wedge T_2} W_{opt}(u) ((\hat{S}_1(u) - \hat{S}_2(u)) - (S_1^n(u) - S_2^n(u))) du$$

since $W_{opt}(\cdot)$ is deterministic and $T_1 \wedge T_2 \xrightarrow{P} \tau = \tau_1 \wedge \tau_2$. Under a sequence of local alternatives $\tau = \tau_c$, so that it's asymptotic efficacy is given by $e(SW^{up})$. Thus $W_{opt}(\cdot) \mathbb{I}[\cdot \leq T_1 \wedge T_2]$ truly yields an optimal SW-statistic for a given S , C_1 and C_2 and sequence of local alternatives specified by D , under these mild conditions.

Such optimal weight functions do not however yield non-parametric statistics, in the sense that for a fixed W_{opt} , weak convergence of SW is not guaranteed for all choices of (S, C_1, C_2) . It is still informative to calculate the optimal weight function and indeed the behaviour of a particular non-parametric SW-statistic can be explained in part by a comparison of the nonparametric weight function with the optimal one.

A nonparametric weight function which we propose for general use is given by

$$\hat{W}_c(\cdot) = \frac{\hat{C}_1^-(\cdot) \hat{C}_2^-(\cdot)}{\hat{\rho}_1 \hat{C}_1^-(\cdot) + \hat{\rho}_2 \hat{C}_2^-(\cdot)}.$$

In uncensored data $\hat{W}_c(\cdot) = 1$ so that the corresponding SW procedure is essentially a generalization of the z-test to censored data. In the following example we compare the behaviour of this SW statistic, and the optimal SW statistic to the locally most powerful test under the proportional hazards alternative with equal censoring distributions, namely the Logrank test.

Example 4.3

Let $S_a(t) = (S_0(t))^{a+1}$, $a > -1$. A sequence of local proportional hazards alternatives is given by $S_1^n(\cdot) = S_0(\cdot)$,

$$S_2^n(\cdot) = S_{a_n}(\cdot) \text{ with } a_n = a \frac{\sqrt{n_1 + n_2}}{\sqrt{n_1 n_2}} \text{ for some constant } a. \text{ For}$$

any t such that $S_0(t) > 0$ then

$$\frac{\sqrt{n_1 n_2}}{n_1 + n_2} (S_1^n(t) - S_2^n(t)) = -a S_0(t) \log S_0(t) + o\left(\frac{\sqrt{n_1 + n_2}}{\sqrt{n_1 n_2}}\right)$$

$\rightarrow -a S_0(t) \log S_0(t) = D(t)$. If $S(t) \log S(t) \rightarrow \pm \infty$ then the convergence is uniform on the set A .

If the underlying survival distributions are Weibull, $S_0(t) = e^{-t^k}$, $k > 0$, then $D(t) = a t^k e^{-t^k}$ and the convergence is uniform on $[0, \infty)$. Simple algebra yields $W_{opt}(t) = t^{k-1}$ in uncensored data and $W_{opt}(t) = 1 + k(t_0 - t)t^{k-1}$, $t \in [0, t_0]$, under equal uniform censoring on $[0, t_0]$. The asymptotic efficacy

of the (most efficient) Logrank statistic is given by

$$e(Lgk) = - \int_0^{\tau} \frac{C_1^-(u) C_2^-(u)}{\rho_1 C_1^-(u) + \rho_2 C_2^-(u)} dS_0(u) \quad (\text{Gill 1980}),$$

so that the asymptotic efficiencies (A.E.) of SW_c and SW_{opt} are given by $e(SW_c)/e(Lgk)$ and $e(SW_{opt})/e(Lgk)$ respectively. These were calculated under a variety of configurations. The results are tabulated in Table 1.

Table 1

Asymptotic Relative Efficiencies under Weibull Proportional Hazards Alternatives

(k, t_0)	AE(W_c)	AE(W_{opt})
(.5, 1)	.98	1.00
(.5, 2)	.99	1.00
(.5, 3)	.99	1.00
(.5, *)	.80	1.00
(1, 1)	.94	1.00
(1, 2)	.97	1.00
(1, 3)	.98	1.00
(1, *)	1.00	1.00
(2, 1)	.87	1.00
(2, 2)	.92	1.00
(2, 3)	.93	1.00
(2, *)	.91	1.00
(3, 1)	.83	1.00
(3, 2)	.87	1.00
(3, 3)	.86	1.00
(3, *)	.84	1.00

* denotes the uncensored case

In all cases examined SW_{opt} is fully efficient and SW_c maintains high efficiency across this broad range of survival

configurations. In the classical exponential scale family with no censoring $W_{opt}(\cdot) = 1 - W_c(\cdot)$ and the z-test is in fact optimal. For values of k greater than unity the z-test loses efficiency in uncensored data. The optimal weight function emphasizes later differences in the survival functions more than early differences and behaves less like $W_c(\cdot) = 1$ as k increases. In censored data the AE of SW_c also decreases as k increases, again because W_c mimics the behaviour of W_{opt} more closely for small values of k than it does for large values.

CONCLUDING REMARKS

From the point of view of the applied statistician the SW-statistics are an intuitively appealing class of statistics for the two-sample survival analysis problem. Motivation for these statistics, results from small sample simulation studies and some ideas on the choice of desirable weight functions from an applied point of view will be presented in a forthcoming paper by the author. Extensions to the k -sample problem have also been developed (O'Sullivan, 1986).

APPENDIX

Lemma A.1

$$T_c \xrightarrow{P} \tau_c$$

unless perhaps if $\tau_i < \tau_{j-1}$, $i = 1$ or 2 , with $S_1(\tau_i) = 0$ and

$$C_1^-(\tau_1) = 0.$$

Proof.

If $\tau_1 = \tau_2$ then since $T_c \in \{T_1, T_2\}$ and $T_1 \xrightarrow{P} \tau_1$ then $T_c \xrightarrow{P} \tau_c$. Thus, suppose $\tau_1 < \tau_2$. If $\tau_c = \tau_2$, then $C_1^-(\tau_1) > 0$ and $S_1(\tau_1) = 0$. Hence, $P[T_c = T_1] \leq P[\hat{C}_1(T_1) = 0] + P[T_1 \geq T_2] \rightarrow 0$ by consistency of $\hat{C}_1(T_1)$ for $C_1^-(\tau_1)$, and $P[T_c = T_2] \rightarrow 1$. In the case that $\tau_1 < \tau_2$ and $\tau_c = \tau_1$ then either $C_1^-(\tau_1) > 0$, $C_1(\tau_1) = 0$ and $S_1(\tau_1) > 0$, or $C_1^-(\tau_1) = 0$. In the former case, $P[T_c = T_2] \leq P[\hat{S}_1(T_1) = 0] + P[T_2 \leq T_1] \rightarrow 0$. In the latter case if we also assume that $S_1(\tau_1) > 0$ then again $\hat{S}_1(T_1) \xrightarrow{P} S_1(\tau_1) > 0$ so that $P[T_c = T_2] \rightarrow 0$, and $T_c \xrightarrow{P} \tau_1 = \tau_c$. The only case remaining is that of $\tau_1 < \tau_2$, $S_1(\tau_1) = 0$ and $C_1^-(\tau_1) = 0$. In general there is no guarantee that T_c converges in this case.

Lemma A.2

If $S = 1 - F$ is an arbitrary right continuous survival function on $[0, \infty)$ and the variance of F denoted by σ^2 is finite, then

$$\sigma^2 = \int_0^\infty \frac{\left(\int_v^\infty S(u) du \right)^2}{S(v)S^-(v)} dF(v)$$

Proof

$$\text{For any } x \in [0, \infty) \text{ let } \sigma_x^2 = \int_0^x \frac{\left(\int_v^x S(u) du \right)^2}{S(v)S^-(v)} dF(v). \text{ Let}$$

$(T_n; n=1, 2, \dots)$ be a sequence of real numbers in $[0, \infty)$ such that

$T_n < T \quad \forall n$, $\{T_n\}$ is increasing and $\lim_{n \rightarrow \infty} T_n = T = \sup\{s: S(s) > 0\}$.

$$\begin{aligned}
 \sigma^2_{T_n} &= \int_0^{T_n} \frac{\left(\int_v^{T_n} S(u) du \right)^2}{S(v) S^{-1}(v)} dF(v) \\
 &= \int_0^{T_n} \left(\int_v^{T_n} S(u) du \right)^2 dS^{-1}(v) \\
 &= \left| \frac{\left(\int_v^{T_n} S(u) du \right)^2}{S(v)} \right|_0^{T_n} + 2 \int_0^{T_n} \frac{\left(\int_v^{T_n} S(u) du \right)}{S(v)} S(v) dv \\
 &= - \left(\int_0^{T_n} S(u) du \right)^2 + 2 \int_0^{T_n} \left(\int_0^v du \right) S(v) dv \\
 &= - \left(\int_0^{T_n} S(u) du \right)^2 + \int_0^{T_n} S(v) dv^2 \\
 \lim_{n \rightarrow \infty} \int_0^{T_n} S(u) du &= \int_0^\infty S(u) du = \int_0^\infty u dF(u)
 \end{aligned}$$

and

$$\lim_{n \rightarrow \infty} \int_0^{T_n} S(v) dv^2 = \lim_{n \rightarrow \infty} \left(\frac{2}{n} S(T_n) + \int_0^{T_n} u^2 dF(u) \right).$$

If $T < \infty$, then

$$\lim_{n \rightarrow \infty} \int_0^{T_n} S(v) dv^2 = T^2 S^{-1}(T) + \int_0^T u^2 dF(u) = \int_0^\infty u^2 dF(u).$$

If $T = \infty$, then

$$\lim_{n \rightarrow \infty} \frac{2}{n} S(T_n) = 0 \quad \text{since } \sigma^2 < \infty$$

and

$$\lim_{n \rightarrow \infty} \int_0^{T_n} u^2 dF(u) = \int_0^{\infty} u^2 dF(u).$$

Hence

$$\lim_{n \rightarrow \infty} \sigma_{T_n}^2 = \int_0^{\infty} u^2 dF(u) - \left(\int_0^{\infty} u dF(u) \right)^2 = \sigma^2$$

But $\lim_{n \rightarrow \infty} \sigma_{T_n}^2 = \int_0^{\infty} \frac{\left(\int_v^{\infty} S(u) du \right)^2}{S(v)S^-(v)} dF(v)$ by the monotone

convergence theorem yielding the desired result. □

References

- Billingsley, P. (1968). Convergence of Probability Measures. Wiley, New York.
- Breslow, N.E., Edler, L. and Berger, J. (1984). A two-sample censored data rank test for acceleration. Biometrics 40,: 1049-62.
- Fleming, T.R., Harrington, D.P. and O'Sullivan, M. (1986). Supremum versions of the Logrank and Wilcoxon statistics. JASA (in press).
- Gill, R.D. (1980). Censoring and Stochastic Integrals. Mathematical Centre Tracts 124. Mathematisch Centrum, Amsterdam.
- Gill, R.D. (1983). Large sample behaviour of the product-limit estimator on the whole line. The Annals of Statistics 11: 49-58.
- O'Sullivan, M. (1986). A New Class of Statistics of the Two-Sample Survival Analysis Problem. Ph.D. Thesis, University of Washington.
- Shorack, G.A. and Wellner, J.A. (1986). Empirical Processes with Applications in Statistics. Wiley.

END

4-~~2~~-87

DTIC